Salisbury NHS Foundation Trust
Drugs & Therapeutics Committee
Summary of
Shared Care Guidelines
And
Monitoring of Disease Modifying Drugs (DMARDs) in ADULTS
June 2017

Rheumatology & Gastroenterology

http://www.icid.salisbury.nhs.uk/Pages/home-l.aspx

Based on The British Society for Rheumatology/BHPR Non-Biologic DMARD Guidance 2016

See also Summary of Product Characteristics or BNF for additional Information

General Information

Disease Modifying Anti-Rheumatic drugs (DMARDs) are added at increasingly early stages in the treatment of rheumatoid arthritis (RA) to suppress the processes responsible for the chronic inflammation of RA, they may be used either as mono-therapy or in combination. DMARDs are also used for the treatment of other rheumatology conditions (e.g. connective tissue disorders and vasculitis) and in other specialities, including dermatology, respiratory medicine and gastroenterology.

A number of these drugs are recommended for prescribing in unlicensed indications. All recommendations are based on the practice of a responsible body of peers of similar professional standing (e.g. The British Society for Rheumatology; see References for full details). Prescribers are advised to discuss with the patient if the medicine is used out of license and document this agreement in the patient's medical record.

These shared care guidelines outline suggested ways in which the responsibilities for managing the prescribing of DMARDs can be shared between the specialist and general practitioner in primary care.

DMARDs should be initiated by hospital specialists only and should not be initiated in the Primary Care setting. GPs are invited to prescribe DMARDs and participate in shared care in accordance to the written instructions given by the Acute Trust Specialists once the patient has reached a stable dose.

If the GP is not confident to undertake these roles, then the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe drugs for this treatment, the GP should reply to this request as soon as practicable.** The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Please consult the manufacturer's Summary of Product Characteristics (SPC) (www.medicines.org.uk) and the current BNF for full prescribing information on contra-indications, side-effects and interactions.

Pre-pregnancy and pregnancy advice

If the patient is pregnant or is thinking of becoming pregnant (in relation to both maternal and paternal patients) then advice should be sought from the originating prescriber.
Further information can also be obtained from **Wessex Drug and Medicines Information Centre, based at Southampton General Hospital.**
The service may be accessed in the following ways:
By telephone: Available from 09h00-18h00 (Mon-Fri), call 023 8120 6908 or 9
By e-mail: medicinesadvice@uhs.nhs.uk

Rheumatology

Consultants/Nurse Specialists Contact via Secretaries		
Rheumatology Reception	01722 429217	8:30 to 16:30
Rheumatology Fax Number	01722 337912	8:30 to 16:30
Patient Adviceline	01722 429137	Ad hoc limited manned hours
Consultant Secretaries , Nurse & OT	01722 345556	di.graham@salisbury.nhs.uk ysanne.cleifr@salisbury.nhs.uk
Dr. S. Bartram		
Dr. Z. Cole		
Dr. A. Coy		
Dr. G.R. Smith		
Dr. S. Bellinvia		
Nurses and OT Secretaries	01722 345556	As above
Senior Nurse Specialist S. Carvalho Nurse Specialist J. Bradford Nurse Specialist T. Donaldson Nurse Specialist C. Gulliver Hand Specialist OT A. Crook Hand Specialist OT J Lee Reis	01722 345556	

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Dr Andrew Tanner	Consultant Gastroenterologist	Andrew.tanner@salisbury.nhs.uk	01722 336262
Dr Christine Blanshard	Consultant Gastroenterologist	Christine.blanshard@salisbury.nhs.uk	01722 336262

Medicines Information (at Southampton Hospital) 023 8120 6908/9

Responsibilities of Speciality Team, GP Team, Pharmacy Team & Patient

Specialist responsibilities

1 Provide patient with information on disease and drug treatment options and explain where drugs are used outside of license.
2 Discuss the benefits and side effects of treatment with the patient and advise women of child bearing age to use reliable contraceptive methods where necessary. Also discuss the effects of the drug on pregnancy if applicable, when the patient may be considering having a family (paternal effects as well) in the future. Also the intention to share care.

3 To confirm the patient has no contra-indications to treatment and consider the relevance of any cautions.

4 Carry out pre-treatment assessment, including height, weight, blood pressure and necessary blood tests (FBC, Creatinine, ALT &/or AST and albumin). Evaluate patient for respiratory disease and screen for occult viral infection.
5 Confirm that the GP is willing to participate in shared care.
6 Ensure the patient knows to report any side-effects or problems to their GP or specialist.
7 The specialist should report any side-effects to the MHRA via the yellow card scheme.
8 Review pre-treatment assessment, including blood test results.
9 Initiate treatment with DMARD and give at least 28 days supply to the patient and give the patient a monitoring booklet/ patient info leaflet as appropriate.
10 Send GP details of baseline assessments and results, prescribed dose of DMARD, monitoring requirements and a summary of the information that has been given to the patient.
11 Advise GP that pneumococcus and influenza vaccinations are recommended in patients taking DMARDs.
12 At first review appointment check initial monitoring results and assess response to treatment.
13 Communicate promptly with the GP when treatment is changed or needs to be changed by the GP, and when any changes in monitoring are required. Ensure that arrangements are in place for GPs to obtain advice and support where needed.
14 Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
15 Ensure that clear backup arrangements exist for GPs to obtain advice and support.

General Practitioner responsibilities

1 Reply to the request for shared care as soon as practicable.
2 Prescribe the DMARD at the dose recommended.
3 Carry out monitoring according to the guideline recommendations.
4 Ensure the patient is aware of any treatment change and that where held, the monitoring booklet is up to date.
5 Report to and seek advice from the specialist on any aspect of patient care that is of concern and may affect treatment.
6 Refer patient to specialist if his or her condition deteriorates.
7 Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
8 Report adverse events to the specialist team and MHRA via the yellow card scheme.

Pharmacist responsibilities

1 Ensure appropriate dose prescribed with clear directions not 'as directed'.
2 Provide advice on adverse effects and any drug interactions with prescription and/or OTC medicines.
3 Issue patient information leaflets where appropriate.
4 Monitor frequency of prescription requests and contact GP if quantities in excess of the prescribed dose are ordered.
5. Advice patient to report any malaise, unexplained bruising or sore throats to Specialist / GP

Patient responsibilities

1. Report to the specialist or GP if he or she does not have a clear understanding or has any concerns in relation to treatment
2. Ensure safe storage and handling of medicine
3. Request repeat prescriptions from GP in good time.
4. Ensure the Pharmacist is aware of the DMARD they are taking prior to purchase of any OTC medicine.
5. Ensure the GP and specialist are aware of any over- the -counter medicines they may be taking.
6. Where patient-held monitoring booklets have been given ensure these are brought to each appointment with their GP or specialist
7. Report any adverse effects to the GP or specialist.
8. Attend blood monitoring appointments

Standard Monitoring Schedule requirements:

For use when starting or adding a new DMARD.

Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every:

- Two weeks until on stable dose for 6 weeks then
- Once on stable dose, monthly FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months.
- Thereafter FBC, creatinine/calculated GFR, ALT, and/or AST and albumin at least every 12 weeks*

*More frequent monitoring is appropriate in patients at higher risk of toxicity (e.g. prior history of adverse drug reactions, patients at extremes of weight, very elderly, impaired renal function and those with co prescriptions of medications that may interact with DMARDS).

Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks then revert back to previous schedule.

Prescribing Information & Monitoring Requirements (ADULTS)

In addition to absolute values for haematological indices a rapid fall or rise and a consistent upward or downward trend in any value should prompt caution and extra vigilance. U/E and creatinine, CRP and/ or ESR should be checked every 6 months. This will enable monitoring of renal disease & disease activity.

DRUG	Indication & dose	Pre-treatment assessment	FBC	U&E, Creatinine	LFT	URINE DipStick Protein	Additional information
Azathioprine **Amber for all indications**	**RA, CTD:** 1mg/kg per day increase at 4-6 weekly intervals to max 3mg/kg per day. **Acute/chronic auto immune hepatitis**: 1-3mg /kg per day **Gastroenterology** Inflammatory bowel disease (unlicensed): 2-2.5mg/kg per day (see additional info)	FBC, U&E, LFT, Creatinine, Chest X Ray (unless done within 6 months). **TPMT assay** -gives additional information on risks of treatment **but does not replace** routine monitoring. Consider screening for Hepatitis B & C & HIV. *Homozygous deficiency* - serious and fatal toxicity- can occur within 6 weeks of starting. *Heterozygous deficiency* - linked to serious adverse events, symptoms may not be evident until 6 months after starting treatment If patient is found to have heterozygous deficiency, monitoring of blood should take place at monthly intervals.	**As per standard monitoring schedule on page 5.**			-	Reduce azathioprine dose to 25% (i.e ¼) of the original when given with allopurinol
Mercaptopurine **Amber** **(Oncology / haematology USE is RED i.e. secondary care only prescribing)**	**Gastroenterology** Inflammatory bowel disease, autoimmune chronic and active hepatitis (unlicensed): 0.75-1.5mg/kg per day	See azathioprine (azathioprine is a prodrug which is converted to mercaptopurine. I*n vivo & m*onitoring requirements are the same) *Note: should NOT be prescribed as 6-mercaptopurine OR 6-MP* Reduce mercaptopurine dose to 25% (i.e ¼) of the original when given with allopurinol					

DRUG	Indication & dose	Pre-treatment assessment	FBC	U&E, Creatinine	LFT	URINE DipStick Protein	Additional information
Hydroxy-chloroquine Amber	**RA, CTD** systemic & discoid lupus erythematosus, photosensitive dermatological conditions 200 – 400 mg daily. Max 6.5mg/kg/day	FBC, U&E, LFT Patients should have a baseline formal ophthalmic examination ideally including objective retinal assessment (e.g. OCT) within 1 year of commencing.	None	None	None	None	Annual review by an ophthalmologist is advised. Discuss with ophthalmologist if treated >5yrs Advise patients to report changes in vision.
Leflunomide Amber	**RA & psoriatic arthritis:** 10mg – 20 mg daily. Maximum 20mg daily when given as monotherapy. Use 10mg daily in combination with other hepatotoxic drugs such as methotrexate	FBC, U&E, LFT, Creatinine. Blood Pressure on 2 occasions 2 weeks apart. If > 140/90 treat before starting Rx Body weight	**As per standard monitoring schedule on page 5** If co-prescribed with another immunosuppressant or potential hepatotoxic agent then blood checks should be continued long-term, **at least once a month.** Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual basis upon discussion with the specialist.				**BP at each visit**. If BP >140/90 treat in line with NICE guidance. If BP remains uncontrolled, stop & consider washout **Weigh at each visit**. If > 10% weight loss with no other cause identified, reduce dose or stop and consider washout. Simple dose reduction is unlikely to produce a rapid decrease of adverse effects (half-life is approx. 2 weeks). If a rapid response is required, consider washout and seek specialist advice

DRUG	Indication & dose	Pre-treatment assessment	FBC	U&E, Creatinine	LFT	URINE DipStick Protein	Additional information
Methotrexate **Amber**	**RA, Psoriasis Psoriatic arthritis, Crohn's disease, connective tissue disease (SLE, myositis, vasculitis), Felty's Syndrome, inflammatory bowel disease (unlicensed):** 7.5 – 25mg ONCE a week. Increase every 2-6 weeks to a maximum dose of 25mg ONCE weekly. (Rarely) max 30mg ONCE week. ONLY prescribe as 2.5mg strength tablets (do not use 10mg tablets) **Rheumatology** s/c route may be given for patients unable to tolerate oral methotrexate. *See sc methotrexate shared care agreement on ICID website:*	FBC, U&E, LFT, CXR (within the last 6 months) Consider screening for Hepatitis B & C & HIV. Chest X Ray (unless done within 6 months). Pulmonary Function Test in selected patients P3NP (procollagen peptide assay) in dermatology patients	**As per standard monitoring schedule on page 5** **Dose increase or unstable bloods:** Repeat every **2 weeks until dose of methotrexate and monitoring stable for 6 weeks,** then return to **standard monitoring schedule** ***Following discussion with the Specialist Team**, it may be appropriate for **selected patients** to be monitored less frequently. i.e. every 2 or 3 months*				• New or increasing dyspnoea or dry cough – withhold and discuss urgently with the specialist team • Avoid prescribing trimethoprim or cotrimoxazole to patients receiving Methotrexate – greatly increases risk of marrow aplasia. • Specialists may recommend co-prescribing of methotrexate and NSAIDs/ aspirin-clinically significant interactions are rare • **Folic acid** given to minimise side effects is usually given 5mg-10mg once weekly, not on the same days as methotrexate; however doses can vary • Ensure patient has a info leaflet/monitoring booklet: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800

DRUG	Indication & dose	Pre-treatment assessment	FBC	U&E, Creatinine	LFT	URINE DipStick Protein	Additional information
Mycophenolate **Amber**	**RA, SLE, lupus nephritis, dermatomyositis, polymyositis:** Start 500mg daily increase weekly by 500mg to optimal or max. tolerated dose. Max – 3g/day.	FBC, U&E, LFT & CXR (within the last 6 months)	**Weekly** until dose stable **for 4 weeks** then **fortnightly for 2 months. Monthly thereafter** even after patient is stabilised on treatment. ***Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis as advised by a specialist.***	**-**	-	-	Advise patients to report any signs or symptoms of bone marrow suppression- inexplicable bruising or bleeding See MHRA Drug Safety Update 14 Dec 2015: Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men
D-Penicillamine **Amber**	**RA, Wilson's disease:** Start 125–250mg/day increase by 125mg, 4 weekly initially to 500mg. Max dose 750mg/day in divided doses	FBC, U&E, Creatinine & Urinary Protein	**Every 2 weeks** until stable for 3 months**. Monthly** thereafter.	**-**	-	**Every 2 weeks** until stable for 3 months. Monthly thereafter	Ask about skin rash or oral ulceration at every visit. Alteration of taste usually settles spontaneously.

DRUG	Indication & dose	Pre-treatment assessment	FBC	U&E, Creatinine	LFT	URINE DipStick Protein	Additional information
Sodium aurothiomalate (Gold) **Amber**	**RA, juvenile idiopathic arthritis.** 10 or 20mg IM stat test dose. Then weekly 50mg, until signs of remission occur. Thereafter decrease frequency to every 2/52 until full remission. Thereafter the interval between injections should be increased progressively as advised by the specialist.	FBC, U&E, LFT, ESR, Creatinine & Urinary Protein	**As per standard monitoring schedule on page 5** Provided blood results are stable, the results of the FBC need not be available before the injection is given but must be available before the next injection, i.e. it is permissible to work one FBC in arrears.			Urinalysis for blood and protein should be carried out just before each injection	Ask about skin rash or oral ulceration at every visit. The patient should remain under medical observation for a period of 30 minutes after drug administration. Toxicity can occur rapidly, if in doubt omit injection and seek specialist advice.
Sulfasalazine **TLS amber**	**RA:** Start at 500mg/day increasing by 500mg weekly to maximum of 2-3 grams/daily (Licensed) *Use Enteric-Coated (EC) sulfasalazine.* **Ulcerative colitis, Crohn's disease**: 1g twice daily increasing to 4g daily in divided doses. *Use plain sulfasalazine.*	FBC, U&E, LFT, Creatinine	**As per standard monitoring schedule on page 5** Repeat **one month** after dose increase. If stable after **1 year** then no routine monitoring needed.				Ask about skin rash, oral ulceration at each visit.

Monitoring - Action to be taken if any of the following applies:

WBC <3.5 x 10^9/l	Withhold until discussed with specialist team
Neutrophils <1.6 x 10^9/l	Withhold until discussed with specialist team
Unexplained Eosinophilia > 0.5x 10^9/l	Withhold until discussed with specialist team
Platelets <140 x 10^9/l	Withhold until discussed with specialist team
Haemoglobin reduction of > 3g/dl	Withhold until discussed with specialist team
ALT &/or AST >100u/L	Withhold until discussed with specialist team ***Leflunomide****- special rules: ALT/AST 2-3x upper limit normal – reduce dose to 10mg,* ***recheck weekly****. If normalized – continue 10mg; if remains elevated withdraw drug and discuss with specialist team. If ALT/AST >3x normal, stop drug,* ***recheck within 72 hours****. If still >3x, withdraw drug and consider washout*. Check other reason e.g alcohol or other medicines or drug interactions
Albumin –unexplained fall (Methotrexate)	Withhold until discussed with specialist team
MCV >105 fl	Investigate (and check if B12 or folate or TSH low start supplementation)
Creatinine > 30% rise from baseline	Repeat in 1 week if still >30% above baseline withhold until discussed with specialist team
Potassium rise to above normal range	Withhold until discussed with specialist team and recheck it remains raised
Urinary protein on dipstick is 2+ (**D-Penicillamine / Gold)**	Send a MSU requesting protein + C&S. If >++ withhold drug. If MSU confirms infection, treat appropriately. If sterile proteinuria – seek advice from specialist team.
Blood pressure >140/90mm Hg (Ciclosporin)	Manage hypertension according to NICE hypertension guidance (Ciclosporin – discuss with specialist team)
Fasting lipids –significant rise (Ciclosporin)	Withhold until discussed with specialist team
Any unexplained illness e.g. nausea/dizziness/headache	If symptoms severe withhold until discussed with specialist team & consider review
Abnormal bruising or sore throat	Withhold until FBC result available
Unexplained acute widespread rash/ hair loss	Withhold – seek urgent specialist (preferably dermatological) advice
New Oral ulceration	Withhold until discussed with specialist
New increasing dyspnoea or cough (methotrexate /leflunomide)	Withhold & discuss urgently with specialist team

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decrease in WBC or albumin or climbing liver enzymes.

November 2011

BSR Statement on Vaccination in Adult Patients with Rheumatic Diseases

http://www.rheumatology.org.uk/includes/documents/cm_docs/2011/b/bsr_vaccination_statement_nov_2011.pdf

Individuals with immunosuppression should be given inactivated vaccines in accordance with national recommendations. It is recommended that patients with autoimmune inflammatory rheumatic diseases should be offered pneumococcal and influenza vaccination.

Vaccination should ideally be administered at least 2 weeks prior to immunosuppression. In individual cases it may be necessary to discuss vaccination with an appropriate local specialist in infectious disease and the patient's General Practitioner. Further advice is available through Public Health England's "Green Book" on Immunisation against Infectious Disease. https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

The vast majority of these vaccinations are given in Primary Care and it is advised that robust local arrangements are instituted to raise awareness both to patients and their General Practitioners of the need for appropriate vaccinations.

BSR is currently updating its guidelines on Disease Modifying anti-Rheumatic Drugs which will include further information in relation to vaccinations in individuals receiving these medications.

For other details related to immunisation:

https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

For specific details relating to Zostavax and patients on DMARDS / Steroids see the ICID website: http://www.icid.salisbury.nhs.uk/MedicinesManagement/JointFormulary/Pages/chapter14.aspx

References

British National Formulary 70 Sept 2015 – March 2016 http://www.bnf.org/

BSR/BHPR Non-biologic DMARD guidelines 2017: https://academic.oup.com/rheumatology/article/56/6/865/3053478/BSR-and-BHPR-guideline-for-the-prescription-and

Electronic Medicines Compendium. Available at: www.emc.medicines.org.uk

Improving compliance with oral methotrexate guidelines. Patient Safety alert 13. National Patient Safety Agency. 1 June 2006. Available via: http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800&p=15

NPSA rapid response report on the risks of incorrect dosing of oral anti-cancer medicines (NPSA/2008/RRR001)

Guidelines for the management of IBD in adults- on behalf of the IBD section of the British Society of Gastroenterology GUT 2011; 60;5, 571-607. http://gut.bmj.com/content/60/5/571.abstract